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I, KIM MARSHALL, MANAGER EXAMINATION SUPPORT AND SALES, hereby certify that the annexed is a true copy of the Provisional specification in connection with Application No. PO 7705 for a patent by AUSTRALIAN INSTITUTE OF MARINE SCIENCE filed on 7 July 1997.

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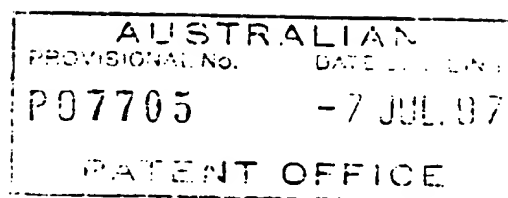
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MANAGER EXAMINATION SUPPORT AND
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Australian Institute of Marine Science

A U S T R A L I A
Patents Act 1990

PROVISIONAL SPECIFICATION
for the invention entitled:

"Prosthetic or Implant Device

The invention is described in the following statement:

- 1A -

"PROSTHETIC OR IMPLANT DEVICE"

FIELD OF THE INVENTION

5

This invention relates to a prosthetic or implant device for medical or related purposes, and in particular to a prosthetic or implant device for use in bone tissue engineering in the field of human medicine, as well as in the non-human veterinary field.

10

BACKGROUND OF THE INVENTION

Crane *et al.* (1995) point out that skeletal deficiencies resulting from trauma, 15 tumours or abnormal development frequently require surgical intervention to restore normal tissue function. Even though current surgical treatments are often successful, all have associated problems with limitations. The limited supply of autograft tissue and the potential of pathogen transfer with allografts have inspired surgeons and engineers to search for other methods to repair skeletal defects. Synthetic materials 20 such as metals and bone cements have also been used for many years, but often result in stress-shielding to the surrounding bone and fatigue failure of the implant.

These authors also point out that recent strategies to engineer bone have focused on the use of natural or synthetic materials as scaffolds for cell transplantation 25 or as conduits to guide new bone growth. The success of the strategy is highly dependent on the properties of the material, requiring minimally that it be biocompatible, osteoconductive, easily sterilized and degradable over an appropriate time-scale into products that can be metabolized or excreted. In addition, scaffolds for cell transplantation must have a high porosity for maximal cell loading, surface 30 characteristics that support cell growth and differentiated function and appropriate pore

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morphology for bone tissue ingrowth *in vivo*. The success of conduits relies on their ability to induce surrounding tissue to invade, grow and replace the implanted material.

A variety of materials are under consideration for use as scaffolds or conduits
5 in accordance with these strategies, however there remains a need for new biomaterial that will interact with living bone tissue and modulate bone formation and repair.

In US Patent No. 3,929,971 (Research Corporation) there is disclosed a synthetic biomaterial having a microstructure substantially corresponding to the
10 microstructure of porous carbonate skeletal material of marine life and made up of hydroxyapatite or whitlockite. This synthetic material is made by converting porous carbonate skeletal material of marine life into a phosphate skeletal material possessing a microstructure substantially the same as or corresponding to the microstructure of the carbonate skeletal source material by subjecting the carbonate skeletal material
15 to hydrothermal chemical exchange with a phosphate.

US Patent No. 4,861,733 (Interpore International) discloses calcium phosphate materials useful as bone substitution material or for the manufacture of prosthetic devices which have been prepared from calcium hydroxyapatite material which has a
20 uniformly permeable microporous structure characterised by a substantially uniform pore volume in the range from about 10 to about 90% and by a pronounced three-dimensional fenestrate structure corresponding to the microstructure of the porous carbonate echinoderm or scleractinian coral skeletal material of marine life, by reacting the calcium hydroxyapatite material which has a calcium to phosphorous atomic ratio
25 of about 1.66 with a phosphate-contributing or phosphorous-contributing moiety or with a calcium-contributing or calcium oxide-contributing moiety so as to alter the calcium to phosphorous Ca/P atomic ratio to yield a calcium phosphate material retaining the above-described microstructure of the porous carbonate echinoderm or scleractinian coral skeletal material but having a calcium to phosphorous Ca/P atomic ratio less than
30 or greater than 1.6.

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Related US Patent No. 4,976,736 (Interpore International) discloses synthetic biomaterials useful for orthopedic dental applications which have a base portion of calcium carbonate and a surface layer of a synthetic phosphate such as hydroxyapatite. The base portion may be a calcium carbonate structure having three-dimensional interconnected porosity such as may be found in porous skeletal carbonate of marine life, e.g. coral porites skeletal aragonite, or it may be porous or non-porous granules of calcium carbonate.

SUMMARY OF THE INVENTION

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According to the present invention there is provided a prosthetic or implant device for medical or related purposes, particularly for use in repair of fracture of a long bone or when elongation of a long bone is required. The prosthetic or implant device of this invention comprises an assembly of shaped members formed from coral, preferably coral of the species *Porites* or *Acropora*, the assembly comprising first and second elongate members each of which is adapted to be fixed at one end to a long bone, the other ends of each of said first and second elongate members being externally and internally threaded, respectively, so that said first member is received by said second member in a threaded inter-engagement.

20

The threaded inter-engagement of the first and second elongate members of the device of this invention enables the overall length of the device to be adjusted to the length required for the particular use, that is in repair of a fracture or in elongation of a long bone, before the device is fixed in place, for example between the ends of a fractured long bone.

25

Preferably, an internally-threaded third member is also provided in threaded engagement with the first member to act as a locking nut and lock the second member with respect to the first member in a desired overall length.

30

Throughout this specification, unless the context requires, the word "comprise" or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

5

DETAILED DESCRIPTION OF THE INVENTION

Coral is the hard deposit consisting principally of calcium carbonate which is built up by minute colonial marine invertebrate animals called coral polyps . The corals
10 of the order *Hydrocoralline* of the Class *Hydrozoa* exist as sessile colonies with a massive encrusting or branching exoskeleton with pits in the surface from which the polyps arise.

The corals of the orders *Alcyonaria* and *Zoantharia* of the Class Anthozoa
15 (Actinozoa) are of different form and habits. Those of the alcyonarians are made up of minute spicules formed within the tissues, occasionally compacted in a hard central rod running through the entire colony and sometimes supplemented by an external covering. Zoantharian corals build up hard deposits externally beneath the basal disk which attaches them to the ocean floor. As new individuals arise from the edge of the
20 living tissue their deposits become continuous with those already laid down and so large colonies produce extensive masses of coral rock. The form of these deposits varies. Some are slender and branching and others rounded and massive. They have received common names such as staghorn coral and brain coral (Van Nostrand's Scientific Encyclopaedia, Eight Edition, Van Nostrand, Reinhold, 1995).

25

Surgical repair of large cortical and other defects, in both humans and non-humans, resulting from traumas or tumour resection presents many challenges. Significant morbidity is associated with autograft harvest sites and the quantity of material available for use in the repair is limited. A bone defect might regenerate more
30 efficiently if a stromal substitute is implanted to provide a framework for organisation

of the osteons. By providing a scaffold containing spaces morphologically compatible with osteons and their vascular interconnections, an association between biocomponents and biologic regenerative and repair responses can be promoted.

5 Each year, a large number of cases involved with bone fractures and deficiencies result in mechanical fixation using temporary or permanent hardware. The use of natural and biodegradable materials for surgical applications can provide strong, biocompatible and degradable hardware that can be manufactured with low cost and may consequently reduce the need for a second surgical intervention following the
10 healing process. It also can be custom fabricated according to special needs. High risk, elderly patients may represent a particular challenge since increasing the need of a second surgical intervention and hospitalization time is crucial. There is a growing search for biocompatible and biodegradable materials for use as hardware for surgical applications.

15

A wide range of metallic, ceramic, polymeric and composite materials have been used in the construction of medical devices for implantation into the human body (Hench and Wilson, 1993). The types of implant can be presented as follows: (1) nearly inert; (2) porous; (3) bioactive; (4) resorbable. Porous structure devices were
20 developed to prevent loosening of the implants. When the porous implant is metal, the large interfacial area can provide a focus for corrosion of the implant and loss of metal ions into the tissue. A film of hydroxyapatite (HA) often coats these, for a more rapid bond of the natural bone to the devices (Hench and Wilson, 1993; Lacefield, 1993; Dunn and Maxiiian, 1994). The coatings, however, often dissolve with time, which
25 limits their effectiveness. In porous implants, it is necessary for the pores to be at least 100 micrometers in diameter to allow capillaries to provide a blood supply to the ingrown connective tissue. It is important to note that interfacial stability is crucial for a clinical successful implantation. Resorbable implants are designed to gradually degrade and be replaced with natural tissue, leading to regeneration of tissue instead

of its replacement. The difficulty is to meet the requirements of strength and short-term and mechanical performance during the processes.

Carbonate skeletons of coral polyp and other reef-building organisms possess
5 a unique microporous lattice structure. This lattice structure promotes ingrowth of connective tissue and eventual bone deposition within the scaffold. Each species of organism governs the microstructural properties of its skeleton to a high degree, however the morphological parameters used to describe the colonies taxonomically do not suffice to characterise them from a materials standpoint. The rationale for using
10 the calcium carbonate structure of coral as a bone substitute material is based on the fact that natural bone is approximately 70% hydroxyapatite by weight and 50% by volume. Porosity and interconnectivity are key factors with respect to the amount and type of ingrowth of tissue into the lattice structure of coral. For example, in highly porous and interconnected implants, tissue ingrowth starts by day three or four. By
15 four weeks, the ingrowth is completed and apposition of bone covering the pore walls has begun. In animal models, bone ingrowth may be nearly complete by three months.

The study of coral as an osseous substitute began as early as 1970s in France
20 and USA. It reflects different ideas and approaches, the first human graft was carried out in 1979 (Patel *et al.*, 1980). One of the early approaches by American researchers was to replicate the porous calcium carbonate skeletal structure of some marine organisms (White *et al.*, 1972). They replicated the microstructure in ceramic, metal, and polymer prosthetic materials in a process that they termed replamineform (White
25 *et al.*, 1972). In another process, using hydrothermal exchange, coral skeletal carbonate was converted to calcium phosphate (Roy and Linnehan, 1974). The result was a compound with good biocompatibility and hardness, its derivatives are still a common material in bone grafting. There is however a continuous debate (Holmes, 1979; Shors and Holmes, 1993; Marchac and Sandor, 1994; Ripamonti, 1996), over
30 the properties of the converted material. It is argued that the conversion process may

cause the coral to lose some of its unique properties that are characterised by its architectural configuration and integration into bone tissue. Both natural and converted coral have undergone some clinical trials and are currently available. Coralline and coralline derivative implants are also under experimental study using animal models
5 (e.g. Glass, 1989; Brain *et al.*, 1993; Ripamonti, 1996) and human clinical trials and evaluation for repair or replacement of broken or diseased bones. Studies are currently being conducted for restoration or replacement of both broken and diseased bone for orthopaedic, cranial, maxillofacial, dental and ocular and orbital floor implants (e.g. Holmes, 1993; Papacharalambous, 1993; Bronzino, 1995; Braye *et al.*, 1996;
10 Mercier *et al.*, 1996).

It has also been suggested that in some cases of mechanical failure of internal fixation for hip fractures, which is common in elderly patients, replacement of lost bone trabeculae may improve the mechanical strength of fixation (Cirotteau, 1993). Holmes
15 (1993) has summarised the main clinical applications for porous hydroxyapatite of marine origin. In most of these cases, solid blocks, rods or granular forms of coralline materials have been used to fill gap and contour defects (Marchac and Sandor, 1994).

It has been noted that the main obstacle in the use of hydroxyapatite and
20 porous coralline materials for load-bearing implants is the relatively poor mechanical properties of these materials, mainly low elasticity and high brittleness, and suggested that future development should focus on the optimisation of properties and microstructural components of the material and impregnation with molecular and cellular agents (Holmes, 1993; Crane *et al.*, 1995; Ashby *et al.*, 1996; Dee and Bizios,
25 1996).

Particularly preferred for use in the prosthetic or implant device of the present invention are two species of corals. The first one, *Porites* is more porous and softer; while the other *Acropora* is stronger, harder and less porous.

I. *Porites*

The entire skeleton deposited by a single polyp or by a colony is the corallum. The skeletons around an individual polyp are corallites and the upper open or end of
5 a corallites is the calyx. The calices are mostly arranged in a hexagonal closed packed array. *Porites* species traditionally have been difficult to distinguish. Confusion results from the fact that some coral species tend to be plastic mainly in response to some environmental parameters such as light intensity, water motion, temperature etc. The plasticity is evidenced by the same species exhibiting a variety of growth forms
10 and colors etc. In most species, the void to solid ratios is generally in the range of 0.4 to 0.6, and the void phase completely interconnects, forming a highly regular network that interpenetrates the solid calcium carbonate phase. In some species, the microarchitecture of the solid and void spaces is nearly identical. The species control regulatory of microstructure characteristics is attractive to material scientists because
15 this uniform and interconnecting architecture has not been matched in man-made, synthetic materials.

Some typical mechanical properties of *Porites* coral

| Property | Test | Orientation | Mean | Range |
|--|---------------------|---------------------------|--------------|------------------------|
| Crush Strength (psi) | Compression | Parallel Perpendicular | 1343 626 | 997-1675 257-963 |
| Ultimate strength (N-cm ⁻¹) | Compression | Perpendicular | 373 | 251-544 |
| Stiffness (N-cm ⁻¹) | Compression | Perpendicular | 8300 | 3310-11470 |
| Energy absorption (N-cm) | Compression | Perpendicular | 9.9 | 4.5-13 |
| Tensile strength (gm-cm ⁻² x 10 ⁴) | 4-point bending | Not reported | Not reported | 2.4-3.3 |
| Young's modulus (gm-cm ⁻² x 10 ⁴) | 4-point bending | Not reported | Not reported | 5.2-6.0 |
| Elastic modulus (dynes - cm ⁻² x 10 ¹⁰) | Resonance frequency | Parallel Perpendicular | 4.8 2.6 | 3.6 - 5.8 1.9 - 3.2 |

20

As shown in Figure 1, some *Porites* species are highly porous and possess a regular and uniform micro configuration (structure) of the skeleton. Colonies can grow to 10m in diameter and can be found in the reef slopes and lagoons. The average density for *Porites* species from the Great Barrier Reef is ~1.4 g/cm³. The average pore size in species growing at outer edge of the Great Barrier Reef is ~200 μ but it can vary between the locations.

II. *Acropora*

30

Acropora species grow widely throughout the tropic seas. The most common growth form of *Acropora* is the branched form with *Acropora grandis* forming staghorn-like colonies. Figure 2 presents a computerised illustration of a typical colony. Branches can be very long (a few metres in height) and as thick as 10-15cm. This species grows 20-25cm a year. Since this species is very common and fast growing,

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samples can be easily collected in sheltered areas of the coral reefs. In addition it is also very easy to culture this species so that collection from the coral reefs can be avoided by use of cultured coral material.

5 The average skeletal density of *Acropora grandis* is $\sim 2.7\text{g/cm}^3$. Because the skeleton of this coral species is dense and strong, it can be easily machined to a variety of configurations of shaped products or structures of different sizes, for example by grinding. This material is particularly suited for use in an implant device, in particular for load bearing bones where strength is an essential property of the implant
10 device.

As previously described, the prosthetic or implant device of the present invention is provided for medical or related purposes. The term "medical or related purposes" is used throughout this specification to include the fields of human and non-
15 human medicine.

The present invention provides a prosthetic or implant device which comprises an assembly of two or more shaped members. Figure 3 shows a typical such device, however it is to be understood that this Figure is included by way of example only.
20

Figure 3 shows an implant device 10 for insertion between the ends 30 and 31 of a long bone (see Fig 3e), for example the ends formed by fracture of the long bone, or when elongation of the bone is needed. Device 10 comprises a threaded male pin 11 (see Fig 3a), an internally threaded female socket 12 (see Fig 3b) and an internally
25 threaded locking nut 13 (see Fig 3c). Fig 4d shows the assembled device 10. As shown in Fig 3a, male pin 11 (which is optionally hollow as shown at 23) consists of an externally threaded shank portion 21 and a head portion 22 which incorporates a socket 24 of suitable dimensions to receive the end of a long bone, which in use of the device will be fixed into the socket, for example using bone cement or similar material
30 or by use of suitable screws, pins or the like. Female socket 12 is internally threaded

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as shown at 25, and is similarly provided with a socket 26 to receive the end portion of a long bone. Locking nut 13 is also internally threaded as shown at 27. It will be evident from Fig 3d which shows the assembled device 10 that the overall length of the device, and hence the distance between the ends of a long bone into which the device is inserted, can be adjusted by screwing the female socket 12 along the shank portion 21 of the male pin 11, and then locking the socket 12 in place with the locking nut 13.

The various shaped members of the device 10 are formed from coral, preferably coral of the species *Porites* or *Acropora*. In work leading to the present invention, offshore coral colonies were collected from the Great Barrier Reef using lifting bags and baskets. The colonies were immediately soaked in a bleaching solution. Since clearing the residual organic matrix is one of the first tasks in the purification process, the first steps were started immediately following collection of the coral. It has been found that by bleaching the colonies immediately after collection and while the colonies were still wet, the best results and cleanest colonies were obtained.

The colonies were then cut into blocks and machined into the desired configurations. After the initial bleaching and cleaning processes, samples were oven dried and kept in a semi-sterile, dry environment to avoid humidity and bacterial infections of the cleaned skeletal materials.

Special holders were fabricated from soft polyvinylchloride polymer material to firmly secure the samples to avoid fractures during the machine processing of the samples.

Oven dried samples were transferred into an hydrostatic pressure chamber where distilled water was pressurised (150psi) into the skeleton, and particularly the fine cavities. This process reduces the amount of dust particles produced and allows easier machining (eg. grinding) of the samples. As an alternative, it has been found

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that dipping samples in liquid nitrogen creates a more solid substrate. After dipping in liquid nitrogen for 2 minutes, processing of the samples was easier and the surface produced by the machine processing was smoother.

5 Finally, the shaped members of the prosthetic or implant device of the present invention may be used to adsorb or bind, and deliver, other therapeutically active substances which assist in the bone repair or regeneration process, or which have other desired therapeutic activity. Such substances include, by way of example, known synthetic or semisynthetic antibiotics which may be introduced into the pore
10 cavities of the shaped members, or a growth factor such as transforming growth factor or one of the bone morphogenic proteins which can be used to assist or promote bone ingrowth.

 Persons skilled in this art will appreciate that variations and modifications may
15 be made to the invention as broadly described herein, other than those specifically described without departing from the spirit and scope of the invention. It is to be understood that this invention extends to include all such variations and modifications.

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Dated this 7th day of July, 1997.

Australian Institute of Marine Science,

By its Patent Attorneys
Davies Collison Cave

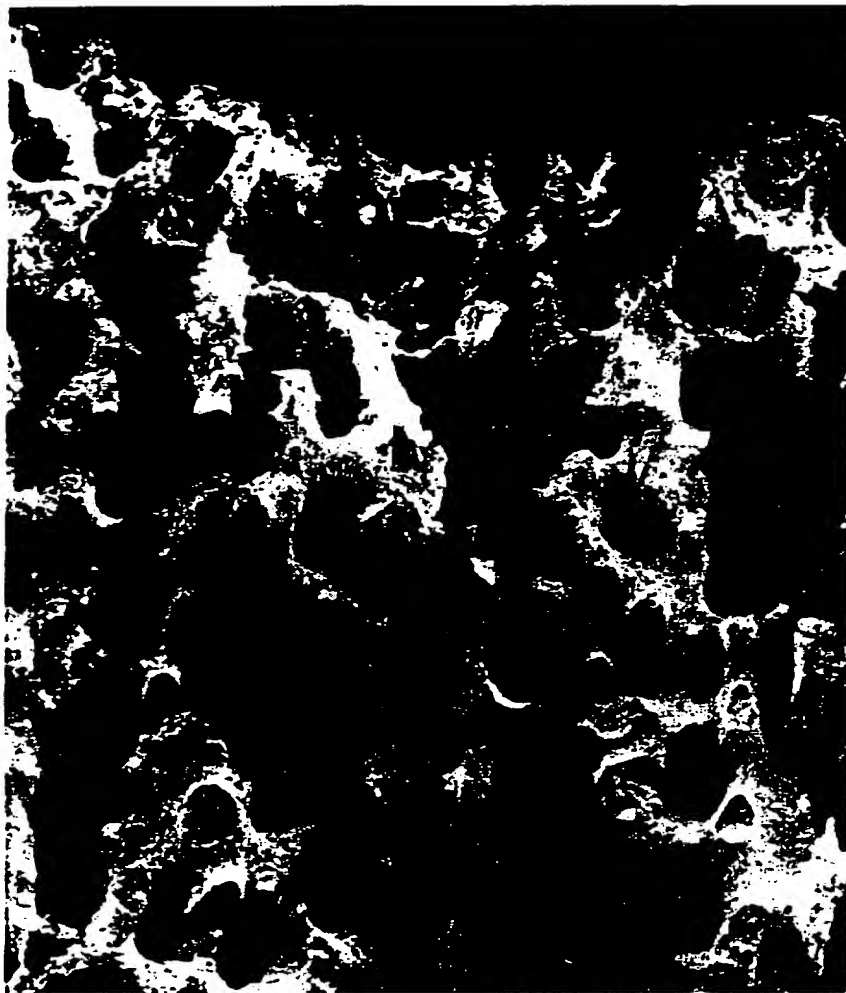


FIGURE 1

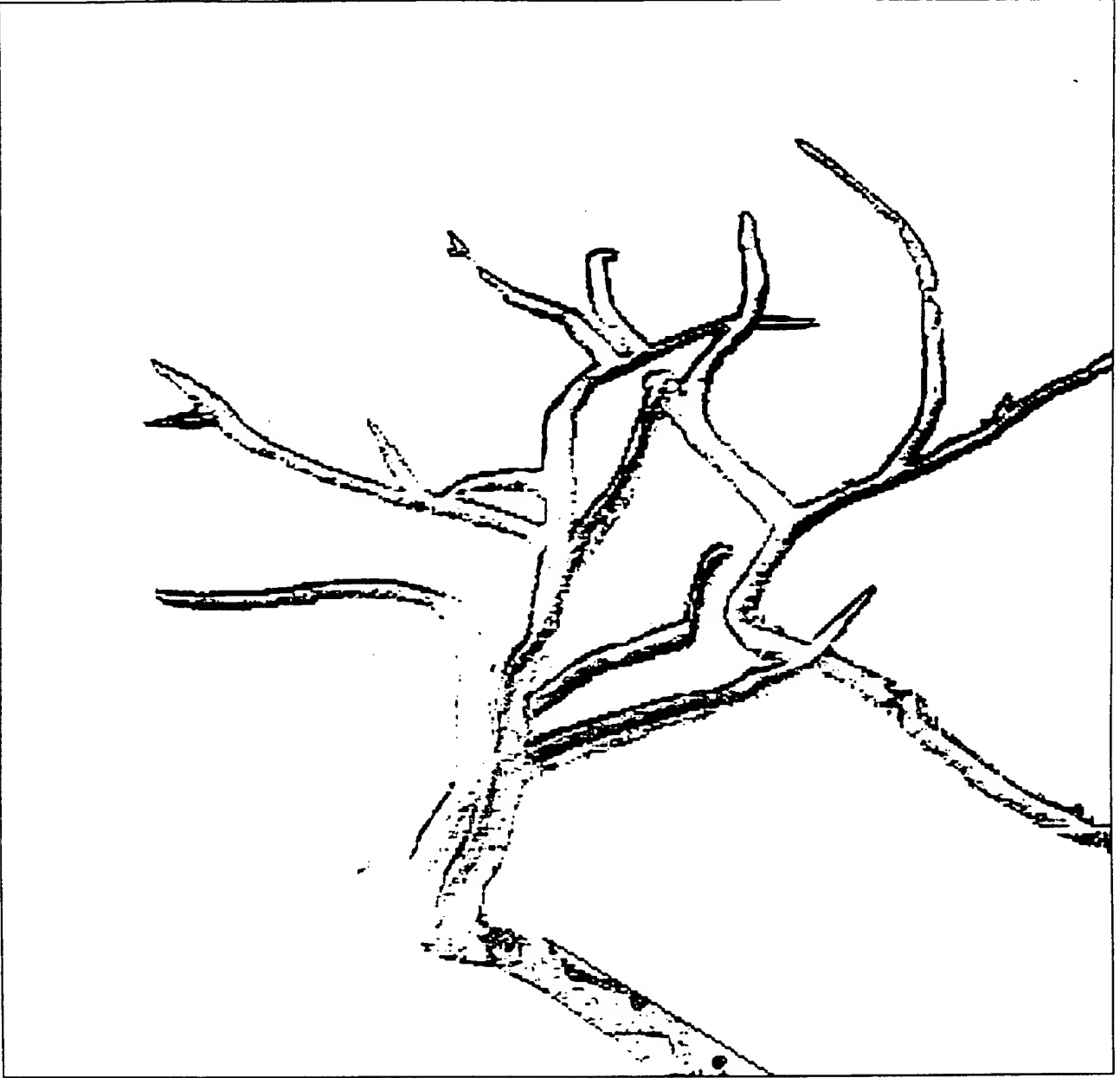


FIGURE 2

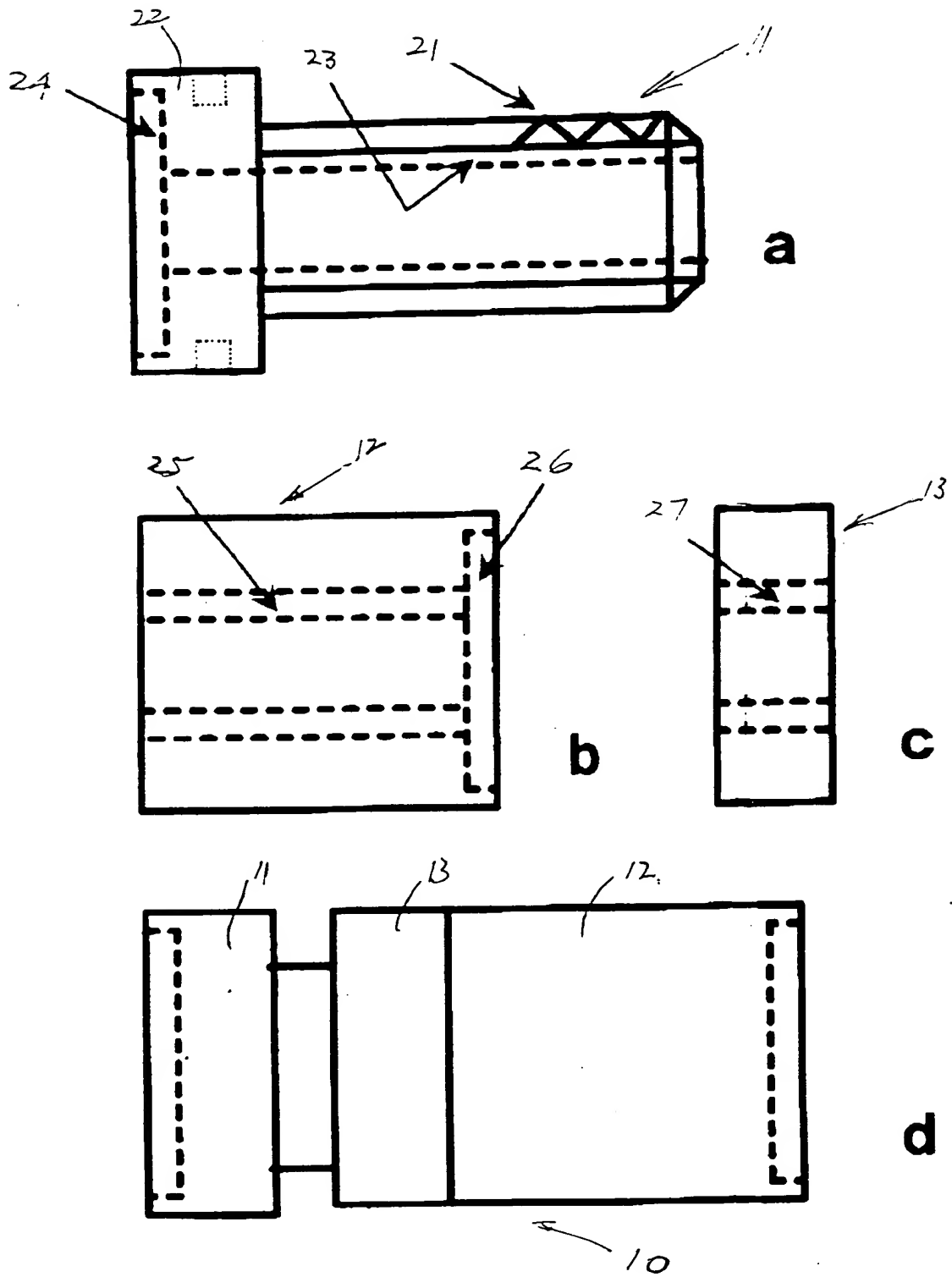


FIGURE 3

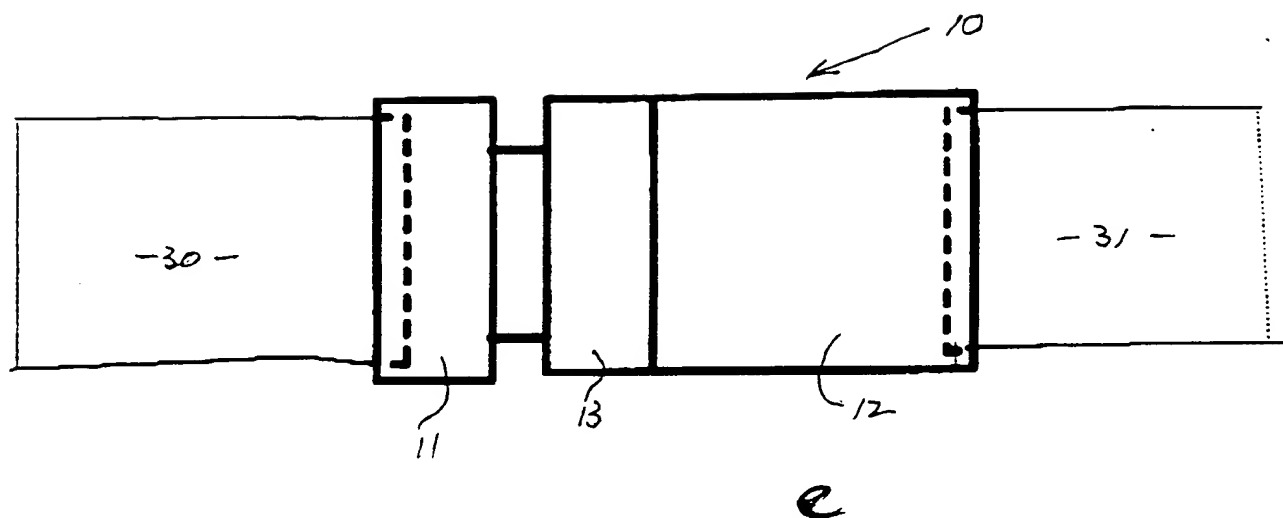


FIGURE 3 (cont'd)